

Clinical usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose in the diagnosis of liver tumors

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We studied various liver tumors by positron emission tomography with fluorine-18 fluorodeoxyglucose (FDG-PET) to examine the diagnostic usefulness of this technique. We also examined the relation between findings on FDG-PET and the characteristics of hepatocellular carcinoma.

FDG-PET was performed in 78 patients with liver tumors, including 53 with primary liver cancer [48 hepatocellular carcinomas (HCC) and 5 cholangiocellular carcinomas (CCC)], 20 with metastatic liver cancer, 2 with liver hemangioma, and 3 with focal nodular hyperplasia. For quantitative evaluation, a region of interest (ROI) was placed over the entire tumor region, at the level of the maximum diameter of the tumor. A background ROI was then placed over the non-tumor region of the liver. The average activity within each ROI was subsequently corrected for radioactive decay, and the standardized uptake value (SUV) was calculated by dividing the tissue activity by the injected dose of radioactivity per unit body weight. SUV ratio was expressed as the tumor-to-non-tumor ratio of the SUV.

The median SUV was significantly lower in HCC than in metastatic live cancer or CCC, and the median SUV ratio was significantly lower in HCC than in metastatic liver cancer or CCC. The median SUV was not higher in multiple HCC than in single HCC, but the median SUV ratio was significantly higher in multiple HCC than in single HCC. The median SUV and the median SUV ratio were significantly higher in the presence of portal vein thrombosis than in the absence of such thrombosis. The Cancer of the Liver Italian Program score and the α -fetoprotein value correlated significantly with both the SUV and SUV ratio. These results suggest that FDG-PET is clinically useful not only for the differential diagnosis of liver tumors but also for evaluation of the clinical characteristics of HCC.

Key words: FDG-PET, hepatocellular carcinoma, cholangiocellular carcinoma, metastatic liver cancer

INTRODUCTION

THE RATE of glycolysis increases in rapidly growing tumors.^{1–4} This increase in glucose metabolism can be quantitatively assessed by positron emission tomography

(PET) with fluorine-18 fluorodeoxyglucose (FDG). DiChiro et al.⁵ measured glucose metabolism in brain tumors with FDG-PET and found a good correlation between the glycolytic rate and the tumor grade. Recent quantitative studies of glucose utilization in liver tumors have shown that dynamic FDG-PET is useful for tumor characterization and assessment of therapeutic response.^{6,7}

We studied various liver tumors by FDG-PET to examine the diagnostic usefulness of this technique. We also examined the relation between tumor characteristics and the finding on FDG-PET in patients with hepatocellular carcinoma (HCC) to evaluate potential clinical applications.

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MATERIALS AND METHODS

Patients

Seventy-eight patients with liver tumors, including 53 with primary liver cancer [48 hepatocellular carcinomas and 5 cholangiocellular carcinomas (CCC)], 20 with metastatic liver cancer [8 arising from the large bowel, 2 from the esophagus, 7 from the pancreas, 1 from the breast, 1 from the uterus, and 1 from the pharynx], 2 with liver hemangioma, and 3 with focal nodular hyperplasia (FNH). The subjects had not been treated before FDG-PET. All tumors were greater than 20 mm in diameter on computed tomographic (CT) images. In patients with HCC, fourteen patients had a single lesion, and the other 34 patients had multiple lesions (2 lesions in 5 patients, 3 lesions in 3 patients, 4 lesions in 3 patients and 5 or more lesions in 23 patients). All patients with CCC had a single lesion, and all patients with metastatic liver cancer had multiple lesions. Diagnosis was established by angiography in 44 patients, biopsy in 21 patients, operation in 7 patients and judgement based on clinical course in 6 patients. These patients ranged in age from 23 to 87 yr. Comparison with CT was made in all patients. Since dynamic CT was not performed in two patients with HCC, comparison with dynamic CT was made in all but 2 patients.

FDG-PET scanning

FDG was produced with an NKK-Oxford superconducting cyclotron and an NKK synthesis system (AMFG01, NKK Co., Muroran, Japan). PET images were obtained by a PET scanner (HEADTOME IV SET-1400W-10, Shimadzu Co., Kyoto, Japan), which has 4 detector rings providing 7 contiguous slices at 13-mm intervals with an intrinsic resolution of 4.5 mm full width at half maximum (FWHM). Images were obtained from 45 to 55 min after intravenous injection of 185–370 MBq of FDG while fasting.

Data analysis

PET images were compared with the corresponding CT images, which permitted accurate identification of the tumor by anatomic landmarks. For quantitative evaluation, a region of interest (ROI) was placed over the entire tumor region, at the level of the maximum diameter of the tumor. Areas of decreased or absent FDG uptake in the tumor, when present, were excluded from the ROI. A background ROI (20 mm × 20 mm) was then placed over the non-tumor region of the liver. The average activity within each ROI was subsequently corrected for radioactive decay, and the standardized uptake value (SUV) was calculated by dividing the tissue activity (in millicuries per gram) by the injected dose (in millicuries) per unit body weight (in grams). Finally, the tumor-to-non-tumor ratio of the SUV (SUV ratio) was calculated. In the case of multiple tumors, SUV was calculated for all tumors,

and the maximum SUV was used.

Characteristics of HCC

The number of tumors, presence or absence of portal vein thrombosis, the α -fetoprotein (AFP) level at diagnosis, and the Cancer of the Liver Italian Program (CLIP) score were studied with respect to the SUV and SUV ratio. The CLIP score is a new scoring system based on both liver function and tumor characteristics that is useful in the prognostic assessment of patients with HCC.⁸ The CLIP score is based on the Child-Turcotte classification (CTC) score, tumor morphology (tumor numbers), the AFP value, and portal vein thrombosis. The CTC score was compared with the SUV of the non-tumor region of the liver. The CTC score, the most widely used index of hepatic functional reserve, was calculated as modified by Pugh et al.⁹

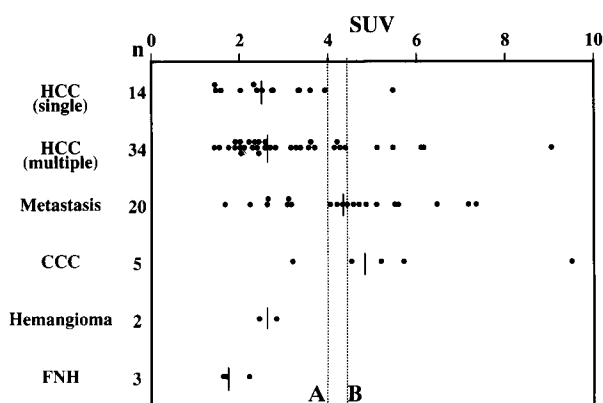


Fig. 1 Standardized uptake values (SUV) in various liver tumors. Vertical lines show median values. Dotted line A (4.0) indicates the position that gave the greatest accuracy for metastatic liver cancer, and dotted line B (4.4) indicates the position that gave the greatest accuracy for CCC.

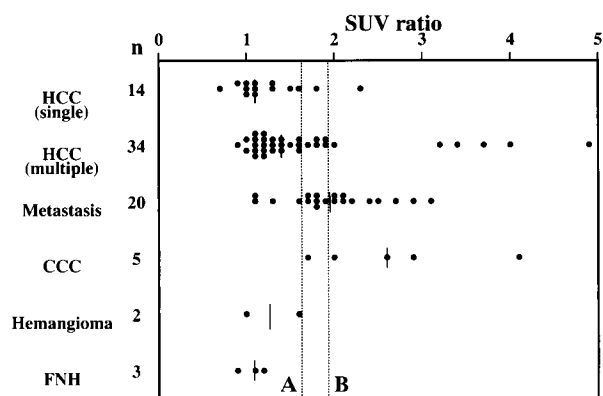


Fig. 2 SUV ratios in various liver tumors. Vertical lines show median values. Dotted line A (1.6) indicates the position that gave the greatest accuracy for metastatic liver cancer, and dotted line B (1.8) indicates the position that gave the greatest accuracy for CCC.

Statistical analysis

Results are expressed as medians with 25th and 75th percentiles. The significance of differences between median values was evaluated by the Mann-Whitney U test (2-tailed). The correlations of SUV and the SUV ratio with AFP, the CLIP score, and the CTC score were analyzed by Spearman's rank correlation analysis. Differences with probability values less than 0.05 were considered significant.

RESULTS

The median (25th and 75th percentiles) SUV was 2.78 (2.02, 3.36) in single HCC and 2.64 (2.10, 4.14) in

Table 1 Sensitivity, specificity, and accuracy for metastatic liver cancer

	Sensitivity	Specificity	Accuracy
SUV	13/20 (65%)	44/58 (76%)	57/78 (73%)
SUV ratio	16/20 (80%)	43/58 (74%)	59/78 (76%)
CT	14/20 (70%)	37/56 (66%)	51/76 (67%)

SUV, standardized uptake value; CT, computed tomography. Numbers of patients are shown, with percentages in parentheses.

Table 2 Sensitivity, specificity, and accuracy for cholangiocarcinoma

	Sensitivity	Specificity	Accuracy
SUV	4/5 (80%)	58/73 (79%)	62/78 (79%)
SUV ratio	4/5 (80%)	56/73 (77%)	60/78 (77%)
CT	1/5 (20%)	51/71 (72%)	52/76 (68%)

SUV, standardized uptake value; CT, computed tomography. Numbers of patients are shown, with percentages in parentheses.

Table 3 Sensitivity, specificity, and accuracy for cholangiocarcinoma in single tumor

	Sensitivity	Specificity	Accuracy
SUV	4/5 (80%)	18/19 (95%)	22/24 (92%)
SUV ratio	4/5 (80%)	18/19 (95%)	22/24 (92%)
CT	1/5 (20%)	15/19 (79%)	16/24 (67%)

SUV, standardized uptake value; CT, computed tomography. Numbers of patients are shown, with percentages in parentheses.

multiple HCC; this difference was not significant ($p = 0.4542$; Fig. 1). The median SUV ratio was 1.12 (0.09, 1.47) in single HCC and 1.37 (1.12, 1.81) in multiple HCC; this difference was significant ($p = 0.0485$; Fig. 2).

The median (25th and 75th percentiles) SUV was 2.64 (2.07, 3.66) in HCC (single and multiple), 4.38 (3.05, 5.31) in metastatic liver cancer, and 5.20 (4.53, 5.71) in CCC (Fig. 1). The median SUV was significantly lower in HCC than in metastatic liver cancer and CCC ($p = 0.0018$ and $p = 0.0081$, respectively). The median SUV ratio was 1.26 (1.07, 1.70) in HCC, 1.90 (1.70, 2.30) in metastatic liver cancer, and 2.55 (1.86, 2.89) in CCC (Fig. 2). The median SUV ratio was significantly lower in HCC than in metastatic liver cancer and CCC ($p = 0.0006$ and $p = 0.0074$, respectively). Dotted line A in Figures 1 and 2 indicates the position that gave the greatest accuracy for metastatic liver cancer, and dotted line B in Figures 1 and 2 indicates the position that gave the greatest accuracy for CCC. The sensitivity, specificity, and accuracy for metastatic liver cancer and CCC are shown in Tables 1 and 2, respectively. Moreover, the sensitivity, specificity, and accuracy for CCC were evaluated in a single tumor of the liver (Table 3).

The median (25th and 75th percentiles) SUV was 2.22 (1.63, 2.83) in benign liver tumors (hemangioma and FNH) and 3.20 (2.34, 4.53) in malignant liver tumors (HCC, metastatic liver cancer, and CCC); this difference was significant ($p = 0.0384$). The median SUV ratio was 1.03 (1.01, 1.21) in benign liver tumors and 1.57 (1.15, 1.96) in malignant liver tumors; this difference was significant ($p = 0.0314$).

The relations of the SUV and SUV ratio to the presence of portal vein thrombosis are shown in Table 4. The median SUV of tumor with portal vein thrombosis was significantly higher than that without portal vein thrombosis, and the median SUV ratio was likewise significantly higher with than without portal vein thrombosis ($p = 0.0004$ and 0.0015 , respectively). The correlations of the CLIP score with the SUV and SUV score are shown in Figs. 3 and 4. The CLIP score correlated significantly with the SUV and SUV ratio ($p = 0.0153$ and 0.0072 , respectively). The correlations of the AFP value with the SUV and SUV ratio are shown in Figs. 5 and 6. The AFP value correlated significantly with the SUV and SUV ratio

Table 4 Relation of the SUV and SUV ratio of tumor to the presence of portal vein thrombosis

	Portal vein thrombosis		p-value
	Present n = 10	Absent n = 38	
SUV	4.33 (3.43, 5.85)	2.41 (2.01, 3.31)	0.0004
SUV ratio	1.88 (1.55, 3.34)	1.20 (1.05, 1.45)	0.0015

SUV, standardized uptake value.

The results are expressed as medians (25th and 75th percentiles).

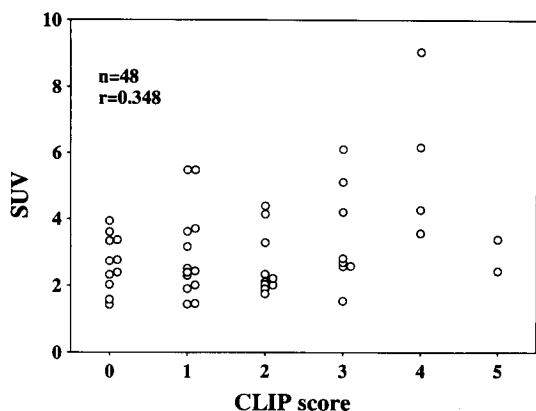


Fig. 3 Correlation between the Cancer of the Liver Italian Program (CLIP) score and SUV.

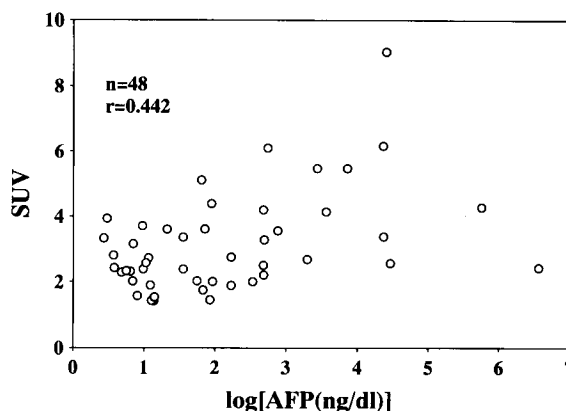


Fig. 5 Correlation between the log[α -fetoprotein (ng/ml)] and SUV.

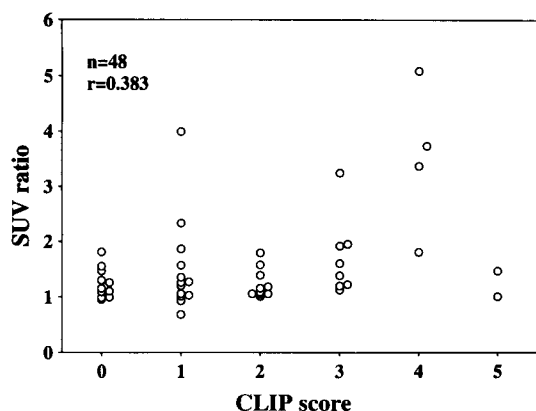


Fig. 4 Correlation between the Cancer of the Liver Italian Program (CLIP) score and SUV ratio.

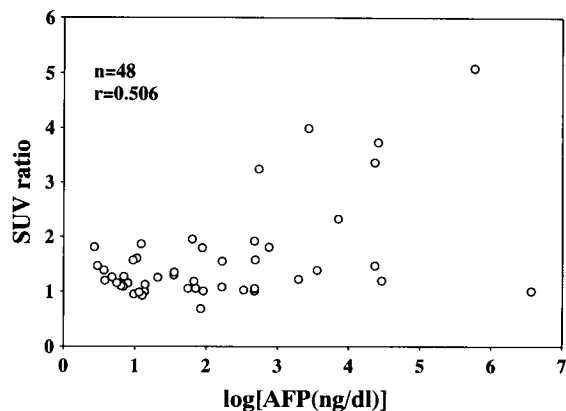


Fig. 6 Correlation between the log[α -fetoprotein (ng/ml)] and SUV ratio.

($p = 0.0019$ and 0.0003 , respectively). The correlation of the CTC score with the SUV of the non-tumor region in the liver is shown in Fig. 7. The correlation was not significant ($p = 0.3455$).

The median (25th and 75th percentiles) SUV of the non-tumor region was 2.29 (1.86, 2.48) in normal liver ($n = 25$) and 2.11 (1.86, 2.43) in cirrhotic liver ($n = 48$); this difference was not significant ($p = 0.1385$). The median blood glucose level in patients with cirrhosis ($n = 48$) was 111 mg/dl (95, 136). The blood glucose level was higher than the normal range (105 mg/dl) in 28 (58%) out of 48 patients with cirrhosis.

DISCUSSION

Ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), angiography, and tumor markers have been used to differentially diagnose liver tumors.^{10,11} We performed FDG-PET in 78 patients with liver tumors and demonstrated that its ability to differentially diagnose these tumors was similar to that of conventional methods.

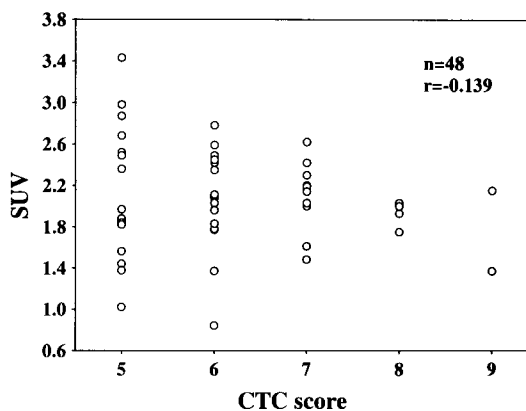


Fig. 7 Correlation between the Child-Turcotte classification score and SUV of non-tumor regions.

The SUV and SUV ratio of liver tumors calculated on the basis of results obtained by FDG-PET differed significantly between HCC and CCC, and between HCC and metastatic liver cancer. The usefulness of FDG-PET for the diagnosis of metastatic liver cancer that has been reported previously,^{7,12-14} is consistent with the results of

our study. We obtained significant differences in both SUV and the SUV ratio between HCC and metastatic liver cancer, and FDG-PET was considered useful as compared with imaging studies, including ultrasonography, CT, MRI and angiography.^{12,15} In our patients, the accuracy of diagnosis of metastatic liver cancer by FDG-PET was higher than that by CT.

Although CCC is considered difficult to diagnose by imaging techniques such as CT,¹⁶ Keiding et al.¹⁷ and Shiomi et al.¹⁸ reported that CCC showed high SUV on FDG-PET. We compared SUV and the SUV ratio for HCC and CCC and found that both values were significantly higher in CCC than in HCC. In our patients, the accuracy of diagnosis of CCC by FDG-PET was higher than that by CT. Furthermore, the accuracy of diagnosis of CCC by FDG-PET was 92% in single tumor of the liver (Table 3), demonstrating the diagnostic usefulness of this technique.

When SUV and the SUV ratio were compared for single HCC and multiple HCC, the SUV ratio in multiple HCC was found to be significantly higher than that in single HCC. This is most likely because multiple HCC is often poorly differentiated, although histological examinations were not done in our study. Previous studies have shown that poorly differentiated carcinomas are associated with active glucose metabolism and a high SUV.¹⁹ Furthermore, AFP correlated significantly with both SUV and the SUV ratio, the latter showing the stronger correlation, in patients with HCC. This stronger correlation with the SUV ratio was probably because most patients with HCC have cirrhosis, and SUV is low in the non-tumor region in the liver, but between patients with cirrhosis and normal subjects there is no significant difference in the values in the non-tumor region of the liver. SUV ratio more strongly correlated with the characteristics of HCC than did SUV, probably because the SUV in the tumor region was affected by the blood glucose level in patients at the time of examination. The blood glucose level is often high in patients with cirrhosis,²⁰ affecting the SUV in the tumor region²¹ so that it does not correlate exactly with the degree of differentiation of HCC. In our study, the blood glucose level was higher than the normal range in 28 (58%) out of 48 patients with cirrhosis. Therefore, the SUV ratio, i.e., the ratio of SUV in the non-tumor region to that in the tumor region, was considered to more closely reflect the characteristics of HCC.

We also examined the correlation of the CLIP score, used to evaluate prognosis in patients with HCC, with SUV and the SUV ratio, and found that the CLIP score significantly correlated with both of these variables. The prognosis of patients with HCC is decided on the basis of the degree of malignancy of the tumor and the functional reserve of the non-tumor region of the liver. Since the SUV in the non-tumor region did not correlate significantly with the CTC score, the prognosis of patients with HCC can be made by using FDG-PET to evaluate the character-

istic of HCC. As the CLIP score includes the AFP value and portal vein thrombosis, the correlation between these two parameters and SUV or the SUV ratio was examined. The AFP value correlated significantly with the SUV and SUV ratio. The median SUV of tumor with portal vein thrombosis was significantly higher than that without portal vein thrombosis, and the median SUV ratio was likewise significantly higher with than that without portal vein thrombosis. Moreover, 9 out of 10 patients with portal vein thrombosis died within one year after FDG-PET.

We therefore consider FDG-PET to be clinically useful not only for the differential diagnosis of liver tumors but also in predicting the outcome in patients with HCC.

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